ANNALS OF SURGERY
Vol. 228, No. 2, 220–227

Staging of the Axilla in Breast Cancer

Accurate *In Vivo* Assessment Using Positron Emission Tomography With 2-(Fluorine-18)-Fluoro-2-Deoxy-D-Glucose

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Objective
To evaluate the ability of positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) to determine noninvasively axillary lymph node status in patients with breast cancer.

Background
The presence of axillary lymph node metastasis is the most important prognostic factor in women with breast cancer. It signifies the presence of occult metastatic disease and indicates the need for adjuvant therapy. The only reliable way in which this important prognostic information may be obtained is by performing axillary dissection, which may be associated with significant complications and delay in discharge from the hospital. PET with ^{18}F-FDG can visualize primary cancers in the breast and metastatic tumor deposits.

Methods
Fifty patients with untreated breast cancer had clinical examination of their axilla performed (graded as positive or negative), followed by PET of the axilla and midthorax. PET data were analyzed blindly and graded as positive or negative, depending on the presence or absence of axillary nodal metastases. Cytopathologic assessment of the axillary nodes was carried out within 1 week of PET, by fine-needle aspiration cytology in 5 patients and axillary dissection in 45; the excised specimens were examined by a single pathologist.

Results
The overall sensitivity of PET in 50 patients was 90% and the specificity was 97%. Clinical examination of the same patients had an overall sensitivity of 57% and a specificity of 90%. In the 24 patients with locally advanced breast cancer (T3, T4, TxN2), PET had a sensitivity of 93% and a specificity of 100%. In T_1 tumors (seven patients), the sensitivity and specificity were 100%. PET had a high predictive value (>90%) and accuracy (94%) in staging the axilla.

Conclusions
PET is a sensitive and specific method of staging the axilla in patients with breast cancer. It may obviate the need for axillary surgery in women with small primary tumors, define the women likely to benefit from axillary dissection, or allow radiotherapy to be substituted for surgery, particularly in postmenopausal women.

Breast cancer is the most common malignancy to affect women, representing 20% of all cancers in women and accounting for 14,000 deaths per year in the United Kingdom.[1] It is widely accepted that axillary lymph node involvement with metastatic tumor is the single most important prognostic indicator in women with breast cancer[2–4] and that a knowledge of axillary lymph node status is necessary for the effective management of patients with this condition. There is no reliable noninvasive method of evaluating regional lymph node status and possible tumor invasion in patients with neoplasms of the breast.[5–12] Surgical removal of axillary lymph nodes does not influence overall survival but is widely practiced to achieve locoregional control of disease and to obtain prognostic data, thus determining any subsequent adjuvant therapy (locoregional or

Supported by the Scottish Home and Health Department, Edinburgh, Scotland.
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Accepted for publication October 22, 1997.

systemic).[13] However, axillary surgery not only delays discharge from the hospital but also can result in significant complications, which may be worsened by subsequent radiotherapy.[14–17] It would be of great benefit (clinically and economically) if a reliable, noninvasive method of determining regional lymph node status could be found and introduced into clinical practice.

Positron emission tomography (PET) produces images based on the biochemical and physiologic processes occurring in the tissues being imaged.[18–21] This is in contrast to conventional imaging modalities, which primarily reflect the anatomic morphology of the structures being visualized. PET uses tracers labeled with short-lived positron-emitting radionuclides. The decay of the latter results in the production of two gamma rays, which are emitted in opposite directions. By recording the simultaneous arrival of pairs of gamma rays in ring detectors surrounding the patient, it is possible to construct a tomographic image of the distribution of the radiotracer. The positron decay process is found in several biologically important elements, such as oxygen, carbon, nitrogen, and fluorine. Thus, a variety of biologic substrates can be labeled with positron-emitting radionuclides while retaining the chemical properties of the parent compound and can, therefore, be followed through various metabolic pathways and biologic processes by this imaging modality.

Malignant cells are known to have a higher glycolytic rate than nonneoplastic cells.[22,23] Therefore, imaging *in vivo* glycolysis, using a positron-emitting substrate, provides an important means of studying the metabolic characteristics of neoplastic tissues. 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) is a positron-emitting glucose analogue that has been shown to be useful in PET studies involving a variety of malignancies.[18–20] In particular, preliminary investigations, with small study populations, of PET using ^{18}F-FDG have demonstrated it to be a sensitive and specific technique for imaging *in vivo* both primary and secondary breast carcinomas.[24–26]

The aim of this study, therefore, was to establish the diagnostic accuracy of PET in the evaluation of the histologic status of axillary lymph nodes in patients with known malignant tumors of the breast.

PATIENTS AND METHODS

Patients

Women attending the Professorial Breast Clinic in Aberdeen Royal Infirmary with a diagnosis of breast cancer were invited to take part in this study. Patients underwent PET imaging of the axilla on the ipsilateral side of the tumor before undergoing treatment. In all patients, a histologic evaluation of the primary breast lesion and axillary nodal status was carried out within 1 week after PET imaging. Patients were deemed ineligible for inclusion in this study if they were younger than 18 years old, were pregnant, had diabetes mellitus, or were unable to lie still within the PET imager. The Joint Ethics Committee of the University of Aberdeen and Grampian Health Board approved the study protocol. Patients were asked to provide informed written consent. Fifty patients were included in this study; their characteristics are shown in Table 1.

PET Imaging

To standardize blood glucose levels, patients were required to fast for ≥6 hours before PET imaging. PET imaging was performed using a Siemens EXACT 31 scanner (Aberdeen PET centre, Aberdeen). This equipment has an axial field of view of 10.8 cm and produces 31 tomographic planes simultaneously with a spatial resolution of 6 mm in the axial and both transaxial directions. Positron emission imaging commenced 40 minutes after the administration of a bolus dose of 185 MBq of ^{18}F-FDG injected into a vein on the arm contralateral to the primary breast lesion. The ^{18}F-FDG was synthesized in the BioMedical Cyclotron Imaging Centre using the method developed by Haaparanta et al.[27]

Patients remained in the prone position with their arms by their sides while in the imager. Imaging was carried out over a 20-cm span below the midpoint of the ipsilateral clavicle to the breast lesion. This required data collection at two bed positions over a 45-minute period, allowing the primary breast lesion, axilla, and internal mammary chain to be imaged.

Image Analysis

The images were analyzed by two experienced observers (PS, FS), without prior knowledge of the patient's clinical assessment, results of staging investigations, surgical find-

Table 1. CHARACTERISTICS OF PATIENTS ENROLLED INTO STUDY

Characteristic	Number
Age (in years)	
Mean	67
Range	26–89
Menopausal status	
Premenopausal	7
Perimenopausal	5
Postmenopausal	38
TNM classification	
T_1	10
T_2	21
T_3	9
T_4	10
N_0	35
N_1, N_2	15
M_0	47
M_1	3

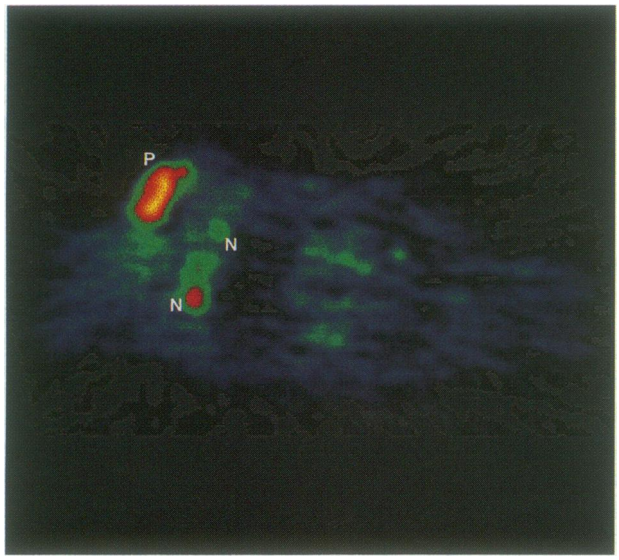

Figure 1. Transaxial PET image. The primary breast tumor is clearly visible (P). Tumor involved axillary lymph nodes can also be seen (N).

ings, or pathologic evaluation. Images were displayed using proprietary software on a personal computer that allowed the observer to display single slices in any of the three orthogonal directions. The data set was initially viewed as a sequence of transaxial slices. Possible abnormal areas were first identified on a slice; using a mouse-controlled cursor, slices could be immediately reconstructed through the abnormality or two other orthogonal directions. Consensus opinion was reached as to the presence or absence of abnormal uptake in the breast and axillary lymph nodes, as well as on the degree of uptake, ranked on a simple three-point scale relative to cardiac uptake. Other significant observations regarding the PET images were also recorded.

Patient Assessment and Treatment

In all patients, a diagnosis of a malignant breast lesion was obtained in the 2 weeks before PET imaging using established triple assessment (clinical evaluation, imaging [mammography, ultrasonography], and fine-needle aspiration cytology). Clinical examination of each patient was repeated immediately before PET imaging by the same clinician (IS). Primary tumor size was measured using calipers and recorded.

The presence or absence of palpable axillary lymph nodes was documented. After PET imaging, patients underwent various investigations to ascertain the extent of disease (liver function tests and liver ultrasound, as indicated; plain radiography of the chest, lumbar spine, and pelvis; and a bone scan). Each patient's breast tumor was classified according to the standard TNM classification.[28] The results of this assessment are shown in Table 1. Most patients underwent primary surgery to the breast (lumpectomy or mastectomy) and axilla (axillary sample [at least four lymph nodes removed] or clearance [level III]).[29,30] Patients with large or locally advanced cancers, and who were scheduled for primary chemotherapy, underwent core biopsy of the breast

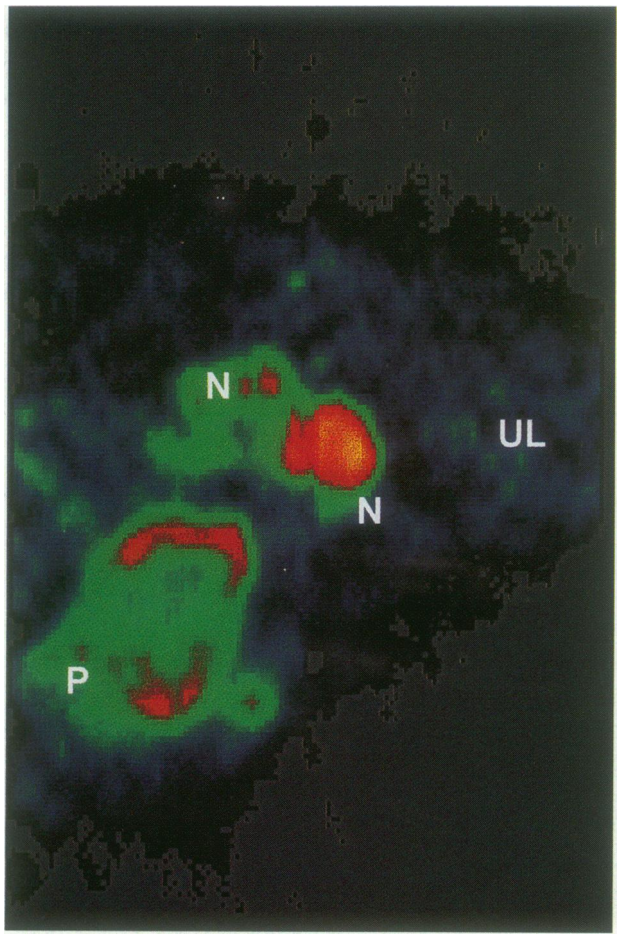

Figure 2. Coronal PET image. Primary breast tumor (P) and tumor axillary nodes (N) are clearly demonstrated. The upper climb is indicated by UL.

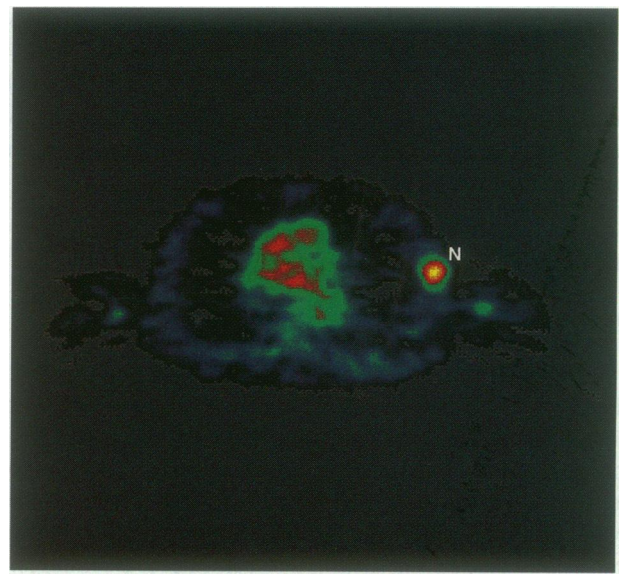

Figure 3. Transaxial PET image showing a tumor involved axillary lymph node (N).

lesion to obtain histopathologic evidence of invasive cancer. All these patients had clinically involved axillary lymph nodes, which were assessed and confirmed with fine-needle aspiration cytology.

Histopathologic Evaluation

Specimens for histopathologic and cytologic evaluation were obtained from each patient's primary breast tumor (core or excision biopsy, mastectomy) and axillary lymph nodes (fine-needle aspiration cytology, axillary sample or clearance) within 7 days after PET imaging. A careful evaluation of the axillary contents was performed to ascertain as accurately as possible the nodal content of the excised axillary specimen. Multiple lymph nodes were embedded in paraffin blocks. Sections of each node were cut at two to four levels, depending on the size of the node. A single pathologist (IM) examined the histopathologic specimens using standard preparation and histochemical techniques.

Statistical Analysis

Sensitivity, specificity, positive and negative predictive values, and accuracy of the PET imaging technique were analyzed using standard statistical analyses.[31]

RESULTS

Histopathology

All 50 patients in this study were known to have malignant tumors in the breast. Two patients had high-grade ductal carcinoma *in situ* with no evidence of an invasive component. Five patients did not undergo primary surgery but had palpable, clinically involved axillary lymph nodes; fine-needle aspiration cytology confirmed the presence of metastatic disease. In these five patients, core biopsy of the breast tumor documented invasive cancer. Axillary dissection was carried out in 45 patients, of whom 21 had lymph node involvement with metastatic tumor on histologic assessment. The pathology of the primary breast tumor was identified by histopathologic examination of the surgical specimen in all 45 patients. These results are summarized in Table 2.

Patient Assessment

Clinical examination established that 15 patients had clinically involved axillary lymph nodes. On histopathologic examination, the axillary nodes from 12 of these 15 patients were found to contain metastatic tumor. Thirty-five patients had no clinical evidence of lymph node involvement. Nine patients in this group of 35 had pathologic evidence of lymph node involvement. Thus, clinical examination (in this group of patients) had an overall sensitivity of 57% and a specificity of 90%. Staging investigations found evidence of distant metastases in three patients. These results are summarized in Tables 1, 3, and 4.

Table 2. HISTOPATHOLOGIC ASSESSMENT

Method of establishing axillary node status	No.
Fine needle aspiration cytology	5
Axillary dissection	45
Total number of axillary nodes examined by dissection	425
Average number of nodes examined by dissection	9
Total number of patients with involved axillary nodes	21
Total number of involved nodes documented in axillary specimens	51
Primary tumor pathology (in all patients)	
Invasive ductal	39
Invasive lobular	3
Medullary	1
Mucinous	3
Tubular	1
Pagets	1
Carcinoma-*in-situ*	2

PET Findings

Thirty patients had no evidence of nodal disease on PET imaging. Of these, 28 patients had no histopathologic evidence of axillary lymph node involvement with metastatic tumor. Data from the PET images in 20 patients documented nodal invasion. One of these patients had no histopathologic evidence of lymph node involvement. These results give PET an overall sensitivity of 90% and a specificity of 97% in the detection of axillary lymph node metastases (see Table 3). When the results of patients who did not undergo primary surgery are excluded, PET had a sensitivity of 88% and a specificity of 97% (see Table 4).

One patient had clinically and pathologically involved axillary nodes but a negative PET scan. Both patients who had negative PET scans but histopathologic evidence of tumor-involved axillary lymph nodes had T2 tumors. These results are summarized in Table 5. If the results from patients with clinically involved lymph nodes assessed by fine-needle aspiration cytology are excluded, all patients who had a single node metastasis identified after axillary node dissection had positive PET scans (see Table 5). The total number of lymph nodes removed from this group of 45 patients was 425 (mean of 9), of which 51 contained metastatic tumor. The smallest metastatic focus of disease identified histopathologically and demonstrated on PET was 0.8 cm in diameter.

Staging investigations revealed evidence of distant metastases in two patients. A chest radiograph in one of these patients demonstrated destruction of the anterior end of one

Table 3. RESULTS OF CLINICAL EXAMINATION AND POSITRON EMISSION TOMOGRAPHY IN ALL PATIENTS

Description	Clinical Examination (n = 50)	Axillary PET Imaging (n = 50)
True-positive	12	19
True-negative	26	28
False-positive	3	1
False-negative	9	2
Sensitivity, %	57	90
Specificity, %	90	97
Positive predictive value, %	80	95
Negative predictive value, %	74	96
Accuracy, %	76	94

PET = positron emission tomography.

left rib, although the bone scan showed no abnormality in this area. The PET image from this patient showed focal uptake of ^{18}F-FDG in the area that corresponded to the abnormality on the chest radiograph. The second patient had evidence of multiple bony metastases throughout the thoracic region on the bone scan. The PET image from this patient demonstrated multiple areas of ^{18}F-FDG uptake corresponding to the abnormal areas on the bone scan. This patient's PET images also showed focal ^{18}F-FDG uptake in the mediastinum.

DISCUSSION

The results from this study show that PET can accurately (94%) and reliably (predictive value >90%) stage the axilla in patients with breast cancer. The overall sensitivity of PET was found to be 90% and the specificity 97% in 50 patients with breast cancer. The study population represents the spectrum of patients who may be encountered in routine clinical practice, although there was a preponderance of patients with large or locally advanced cancers. If the patients with locally advanced breast carcinoma are considered in isolation, PET was found to have a sensitivity of 93% and a specificity of 100%.

In three patients studied, PET gave erroneous results. Two patients had histopathologic evidence of axillary lymph node metastases but negative PET scans. One of these patients had clinically palpable lymph nodes. Both patients had T2 tumors in the upper outer quadrant of the breast. The levels at which the involved lymph nodes were present in the axilla are difficult to establish. Both of these patients had lymph node metastases whose sizes were within the imaging resolution of PET (25 mm and 12 mm). A possible reason for the erroneous results is patient positioning in the imager. While in the imager, patients were positioned with their arms by their sides. This may have made it difficult to differentiate level I axillary lymph nodes from breast tumors in the upper outer quadrant. We propose, in subsequent studies, that patients position their hands behind their head while undergoing imaging. One patient with a positive PET scan had no histopathologic evidence of lymph node involvement by metastatic tumor. On pathologic examination of the surgical specimen, six lymph nodes were identified; the primary tumor measured 2 cm in

Table 4. RESULTS OF CLINICAL EXAMINATION AND POSITRON EMISSION TOMOGRAPHY IN PATIENTS WHO RECEIVED AXILLARY DISSECTION

Description	Clinical Examination (n = 45)	Axillary PET Imaging (n = 45)
True-positive	7	14
True-negative	26	28
False-positive	3	1
False-negative	9	2
Sensitivity, %	44	88
Specificity, %	90	97
Positive predictive value, %	70	93
Negative predictive value, %	74	93
Accuracy, %	73	93

PET = positron emission tomography.

Table 5. POSITRON EMISSION TOMOGRAPHIC RESULTS AND TNM TUMOR STAGING

TNM Stage	Axillary PET Results					
	True Positive	True Negative	False Positive	False Negative	Sensitivity %	Specificity %
T_1	1	7	0	0	100	100
T_2	7	11	1	2	78	92
T_3	5	4	0	0	100	100
T_4	6	4	0	0	100	100
N_1 and N_2	10	3	0	1	91	100
T_3, T_4, T_xN_1, T_xN_2	14	10	0	1	93	100

diameter. The technique we use to sample the axilla is that documented by Steele et al.[29] This is an accurate and well-validated surgical procedure with a low error rate.[30] An audit of our practice (approximately 275 breast cancers per annum) has documented that the incidence of axillary recurrence is low (<1%) on 5-year follow-up (unpublished findings). Therefore, we believe that in this case it was the PET result that was incorrect rather than a deficiency of surgical staging.

Several groups of investigators have postulated that PET using ^{18}F-FDG may be a useful method of noninvasively staging the axillae of patients with breast cancer, with reported sensitivities ranging from 57% to 100% and specificities from 66% to 100%. The published data are summarized in Table 6. However, in most publications, the study populations evaluated have been small. The present comprehensive evaluation of PET using ^{18}F-FDG confirms that this imaging modality is indeed an accurate method of noninvasively staging the axillae of patients with malignant breast neoplasms and, as such, may have several important clinical applications in the management of patients with breast cancer.

As previously stated, a knowledge of axillary lymph node status is essential to plan appropriate systemic adjuvant therapy, particularly in premenopausal women. At present, this information is obtained by carrying out some form of axillary dissection. However, surgery to the axilla is associated with a not insignificant morbidity rate (*e.g.*, lymphedema, cellulitis, neurovascular damage, impaired shoulder mobility), delay in hospital discharge, and prolonged postsurgical rehabilitation.[14,17,32,33]

It has been suggested that axillary surgery may be avoided or minimized in subgroups of patients who are unlikely to have lymph node metastases (*i.e.*, those with small primary tumors or noninvasive disease).[34–38] However, this approach may result in metastases remaining *in situ* in up to 25% of patients with small invasive cancers and, thus, the loss of important prognostic information.[39] An imaging modality that could noninvasively identify patients without involved axillary nodes would be of great clinical benefit. In the present study, PET of the axilla had a sensitivity and specificity of 100% in the seven patients who had clinical T1N0 tumors and the two patients who had noninvasive disease. However, a study conducted by Avril et al.[40] demonstrated a sensitivity of only 33% in 18 patients with pathologic stage T1 tumors. Therefore, more of such patients need to be evaluated before a conclusion can be made regarding the use of PET as an alternative approach to surgery in this group of women.

In an attempt to minimize the complications resulting

Table 6. PET STUDIES PUBLISHED, EVALUATING AXILLARY LYMPH NODE STATUS

Study	True Positive	True Negative	False Positive	False Negative	Sensitivity (%)	Specificity (%)
Minn et al. (1989)[24]	6	8	1	3	75	89
Wahl et al. (1991)[56]	3	NA	NA	NA	NA	NA
Tse et al. (1992)[57]	4	7	0	3	57	100
Nieweg et al. (1993)[58]	5	NA	0	0	NA	NA
Hoh et al. (1993)[59]	6	5	0	3	67	100
Adler et al. (1993)[51]	9	14	1	1	90	93
Bassa et al. (1996)[60]	10	3	0	3	77	100
Avril et al. (1996)[40]	19	26	1	5	79	96
Adler et al. (1997)[61]	19	21	11	1	95	66
Sceidhauer et al. (1996)[62]	9	8	1	0	100	89

PET = positron emission tomography; NA = not applicable.

from axillary surgery, limited forms of axillary dissection have been carried out (*e.g.*, sentinel lymphadenectomy, axillary sample or level I axillary dissection).[29,41,42] However, it has been reported that some patients with uninvolved level I nodes have metastatic tumor in nodes at levels II and III.[43–47] Therefore, there is a likelihood that low axillary dissections, particularly if not performed according to validated criteria,[29,30] may fail to determine true nodal status. Sentinel lymph node biopsy, guided by surgical vital dye infiltration of tumor or presurgical infiltration with gamma ray-emitting agents,[48] has been less reliable in staging the ipsilateral axillary lymph nodes in breast cancer than in melanoma because of biotechnologic difficulties with these techniques. On the evidence obtained to date, PET could help determine treatment options in postmenopausal women, accepting that approximately 5% of patients would have unnecessary radiotherapy to the axilla (in the absence of surgery) and up to 10% may have axillary "recurrence" in due course (in the absence of any form of treatment). In patients properly informed, counseled, and carefully evaluated, such an approach may be justified, particularly with small tumors.

Primary chemotherapy has an important role in the management of patients with locally advanced breast cancer. It is widely used both to downstage the primary tumor and to treat occult systemic metastases before local surgery. The presence of metastatic tumor in regional lymph nodes after a course of neoadjuvant chemotherapy is of considerable prognostic importance.[2] Evidence suggests that tumor cells that metastasize have a lower sensitivity to systemic chemotherapy than cells that remain *in situ* in the breast.[49,50] Thus, the ability to identify metastatic tumor in patients with locally advanced breast cancer and monitor its response to cytotoxic agents may be of considerable benefit. The present study showed that PET imaging of the axilla had a sensitivity of 93% and a specificity of 100% in patients with large or locally advanced breast cancers. Previous published studies have also demonstrated the ability of PET imaging to identify metastatic tumor in patients with large breast neoplasms.[40,51] If appropriate quantitative imaging techniques are used, PET may be used to monitor malignant tumor response to cytotoxic therapy.[52–54] This may prove to be one of the most important applications of PET imaging in the management of patients with breast cancer.

In the present study, PET provided additional information about the extent of disease in 2 of the 50 patients imaged. Similar cases have been reported in the other previously published investigations.[40,55] PET, therefore, may have the advantage of obviating the need for additional staging investigations when used to image patients with breast cancer.

In summary, PET appears to be the most accurate and reliable noninvasive method of determining axillary lymph node status in patients with breast cancer and, thus, may either obviate the need for or selectively define women (particularly postmenopausal women) who require axillary surgery. PET may also have an important role in the management of patients with locally advanced breast cancer receiving primary chemotherapy—for example, in determining the duration of treatment and the most efficacious regimen.

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